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Underdiagnosis of influenza virus infection in hospitalized older adults

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Abstract

Objective—To describe factors associated with provider-ordered influenza testing among hospitalized adults.

Design—Information on patient demographics, symptoms, and provider-ordered influenza testing were collected by questionnaire and chart review. We conducted prospective laboratory-based surveillance using reverse-transcriptase polymerase chain reaction (RT-PCR), the gold-standard for diagnosis of influenza, to determine how patient characteristics and provider-ordered testing impacted accurate influenza diagnosis.

Setting—One academic and three community hospitals in Davidson County, Tennessee, USA.

Participants—1422 adults ages 18 years and older with acute respiratory illness or non-localizing fever.

Measurements—We compared characteristics of participants with and without provider-ordered testing for influenza using the Wilcoxon test and Pearson's chi-square test. Multivariable logistic regression models identified factors predictive of provider-ordered influenza testing.

Results—Overall 28% (399/1422) of participants had provider-ordered influenza testing. Patients who were tested were younger than those not tested (58 ± 18 years vs. 66 ± 15 years, $p < 0.001$)

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Conflict of interest YZ and LH have no conflicts of interest.

Author contributions Hartman: interpretation of data, drafting and revision of manuscript. Talbot: study design, interpretation of data, revision of manuscript. Zhu: study design, interpretation of data and critical review of manuscript. Edwards and Griffin: critical review of manuscript. All authors approved the final version of the manuscript.

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and more likely to have influenza-like illness (ILI, 71% vs. 49%, $p < 0.001$). ILI increased with decreasing age: 48% ≥ 65 years; 60% 50–64 years; and 63% 18–49 years. Among all patients, presence of ILI and younger age were independent predictors of provider-ordered testing. Among the 136 patients with RT-PCR confirmed influenza, ILI was the only significant predictor of provider-ordered testing (AOR 3.43, 95% CI 1.22–9.70).

Conclusion—Adults 65 years and older hospitalized with fever or respiratory symptoms during influenza season are less likely to have a provider-ordered influenza test than younger adults. Some, but not all, of this disparity is due to a lower likelihood of ILI presentation. Further strategies are needed to increase clinician awareness and testing in this vulnerable group.

Keywords

influenza; elderly; older adults

Introduction

Infections caused by influenza virus are associated with substantial morbidity and mortality for all age groups, with the highest rates of hospitalization and death in older adults [1–6]. Prompt recognition, diagnosis, and treatment is predicated upon a suitable case definition of influenza-like illness (ILI), conventionally defined by the Centers for Disease Control as fever (temperature ≥ 37.8°C) and cough and/or sore throat [7]. However, this definition has several limitations in older adults due to both co-morbid conditions and immune senescence (aging of the immune system). Adults ≥ 65 years may have an attenuated febrile response, potentially due to altered thermoregulatory responses or lower baseline core body temperatures, leading some to suggest revised criteria with a lower fever threshold for older adults with suspected influenza [8–12]. Recognition of influenza in older adults may be further complicated by cognitive deficits that limit ability to communicate symptoms and exacerbations of chronic conditions, particularly cardiac and pulmonary disease, that may dominate the clinical presentation. The impact of these differences on provider-ordered influenza testing is not well known.

We examined the demographic and clinical characteristics of inpatients that underwent provider-ordered influenza testing and compared them to those who were not tested to examine what factors influence influenza testing. Since all patients underwent study-ordered RT-PCR testing for influenza, patients with study-confirmed influenza were compared with those who underwent provider-ordered testing to examine what impact testing behaviors had on diagnosis and treatment of influenza virus infections across age groups, particularly in the ≥ 65 year old population.

Methods

Study Design

Adults hospitalized with symptoms of acute respiratory illness or non-localizing fever at four hospitals in Davidson County, Tennessee were enrolled during each influenza season from November 2006 to April 2012 with the primary goal of evaluating the effectiveness of influenza vaccine for the prevention of hospitalization. The influenza season was defined as weeks including all laboratory-confirmed influenza infections in the clinical and research laboratories at Vanderbilt University Medical Center. Two hospitals collected surveillance data during the first two influenza seasons, and four hospitals (one academic and three community hospitals) collected data from 2008 to 2012. The 2009 pandemic season was excluded from analyses.

After consent and enrollment in the study, the patient or his/her caregiver completed a questionnaire regarding presenting symptoms and influenza vaccination status. Patients with respiratory illness or fever were further classified as presenting with ILI based on symptoms of cough and/or sore throat and fever (temperature ≥ 37.8°C or subjective report of fever or feverishness). Healthcare providers were unaware patients were enrolled in the study, hence any inpatient influenza testing by providers was ordered as part of usual care. Medical records were reviewed using a standardized form to obtain demographic information, history of comorbid medical conditions, results of provider-initiated diagnostic studies, and discharge diagnoses. Provider-ordered influenza tests included rapid antigen detection, polymerase chain reaction (PCR), or viral culture tested in the clinical laboratory of their respective institution.

The study protocol was approved by the Institutional Review Board of Vanderbilt University Medical Center and the private Institutional Review Boards Sterling and Western.

Study Population

Patients hospitalized with the following admission diagnoses (International Classification of Diseases, 9th Revision) were enrolled: pneumonia (480–486), upper respiratory infection (465), bronchitis (466), influenza (487), chronic obstructive pulmonary disease (490 to 492; 496), asthma (493), viral illness (079.9), dyspnea (786), acute respiratory failure (518.81), pneumonitis due to solids/liquids (507), or fever (780.6) without localizing symptoms or if patients presented with any of the following symptoms: cough, non-localizing fever, shortness of breath, sore throat, and nasal congestion or coryza. Adults 50 years of age and older were enrolled for the first two influenza seasons, and adults ≥ 18 years were enrolled from 2008 onwards.

Laboratory Methods

Mid-turbinate nose and throat swabs were obtained from each patient at the time of enrollment and tested for influenza virus in the research laboratory by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) using primers and probes designed by the Centers for Disease Control and Prevention. Confirmed study-ordered influenza positive cases were defined as positive RT-PCR on duplicate testing of the individual's sample.

Analysis

We compared characteristics of subjects with and without provider-ordered testing for influenza using the Wilcoxon test and Pearson's chi-square test for continuous and categorical variables, respectively. The following variables were pre-specified as potential factors impacting provider-ordered influenza testing: age (as a continuous variable), race, insurance, underlying medical comorbidities (cardiac disease, COPD/asthma, and other high-risk conditions), ILI, self-reported vaccination status, and study year. Two multivariable logistic regression models were conducted to assess associations between pre-specified factors, provider-ordered influenza testing and study-ordered influenza positive patients. Adjusted odds ratios and 95% CIs were reported. All data analyses were conducted using the statistical computing program R version 3.4.1.

Results

Patient Characteristics

A total of 2556 adults hospitalized with symptoms of acute respiratory illness or non-localizing fever were eligible for the study, of whom 1422 (56%) consented to participate (table 1). Although the average age of those who participated was lower than those who declined participation (63 vs. 67 years; $p < 0.001$), enrolled participants were similar to those who declined participation in regard to sex (60% vs. 57% female) and race (39% vs. 40% white). Of the 1422 enrolled participants, 48% were aged 65 years and greater, 39% were white and 10% were black.

Provider-ordered influenza testing

Provider-ordered influenza testing included antigen detection, viral culture, PCR, or a combination and was ordered in only 28% (399/1422) of enrolled subjects presenting with an acute respiratory illness or fever. Overall 41% (231/561) of participants receiving care in the academic hospital had provider-ordered testing for influenza compared to only 20% (168/861) in the community setting. Of the total of 450 provider-ordered tests, 387 (97.0%) were antigen detection, 29 (7.3%) were viral culture, and 34 (8.5%) were PCR detection. Among those who had provider ordered testing, 8% (32/399) of patients had clinical laboratory confirmed influenza, representing 2% (32/1422) of the total population. Among those who had research laboratory testing, 10% (136/1422) of patients had research laboratory confirmed influenza, including 77 patients tested for influenza by their physician and 59 patients not tested, with 43% (59/136) of the patients with confirmed influenza by RT-PCR not tested by their providers. There was no significant variation in proportion of patients tested by month or season during the influenza seasons included in this study [13].

Provider-ordered testing was more common among younger patients and in those presenting with ILI (table 2). The mean age of those with vs. without provider-ordered influenza testing was 58 ± 18 years vs. 66 ± 15 years, respectively ($p < 0.001$). Among the patients who presented with ILI, the mean age of those with vs. without provider-ordered influenza testing was 55 ± 10 years vs. 63 ± 9 years, respectively ($p = 0.027$). Duration of symptoms on admission was similar in those with provider-ordered testing compared to those who were not tested (4.2 ± 7.0 days vs. 4.8 ± 7.5 days, $p = 0.15$).

Those with provider-ordered influenza testing were more likely to have presented with fever (73% tested vs. 44% not tested, $p < 0.001$) and ILI (71% tested vs. 49% not tested, $p < 0.001$). Among all patients, ILI was less common in older patients (48% ≥ 65 years; 60% 50–64 years; and 63% 18–49 years). Among patients with study-confirmed influenza, ILI was also less common in older patients (74% ≥ 65 years; 83% 50–64 years; and 81% 18–49 years).

Provider-ordered testing did not differ by patient gender or race. A significantly lower proportion of patients with heart disease and lung disease, including COPD or asthma, underwent provider-ordered influenza testing when compared to those without these conditions (36% vs. 64%, $p < 0.001$ and 45% vs. 55%, $p < 0.001$, respectively). There was no significant difference in comorbid cardiac or pulmonary disease between provider tested and not tested patients who presented with ILI. A greater proportion of those not tested for influenza reported having had been vaccinated compared to those tested (69% vs. 61%, $p = 0.005$). The distribution of discharge diagnoses for those tested vs. not tested for influenza differed significantly ($p<0.001$): while both groups were primarily diagnosed with pneumonia (37% not tested vs. 41% tested), those not tested for influenza were discharged with proportionally more diagnoses of COPD/asthma (30% vs. 20%) and cardiac disease (11% vs. 3%).

In patients presenting with an acute respiratory illness during influenza season, independent factors associated with provider-ordered influenza testing in a multivariable logistic regression model were younger age (AOR 2.02, 95% CI 1.55–2.63), no history of lung disease (AOR 1.68, 95% CI 1.26–2.24) and symptoms of ILI (AOR 2.22, 95% CI 1.71–2.89) (table 3). In a model of only those patients with confirmed influenza by study-ordered influenza testing, only ILI was a significant independent factor associated with provider-ordered influenza testing (AOR 3.43, 95% CI 1.22–9.70). Finally, those with provider-ordered testing were more likely to receive treatment with antivirals (6.8% vs. 0.2%, $p < 0.001$).

Discussion

In our study, provider-ordered testing for influenza was uncommon, and nearly half of the patients with confirmed influenza by RT-PCR did not have testing ordered by their providers. Patients who were tested for influenza by their providers tended to be younger and to have presented with ILI. A lower proportion of older adults presented with ILI compared to younger adults, consistent with prior studies examining clinical case definitions for influenza [8–10, 14, 15]. In our analysis of independent factors associated with influenza testing, age was negatively correlated with provider-ordered testing. For those patients who had study confirmed influenza by RT-PCR, only ILI was correlated with provider-ordered testing. The known lack of ILI symptoms in older adults may lead to missed influenza diagnosis and missed opportunities for treatment. However, we found that even in the subset of older patients who presented with ILI, fewer had provider-ordered influenza testing than younger adults, and though the interaction between age and ILI was not statistically significant it suggests that ILI presentation alone may not account for decreased testing.

Those with cardiac and/or pulmonary disease were also less likely to have provider-ordered influenza testing, which may simply reflect the many alternative diagnoses that exist for respiratory illness in patients with underlying disease. However, it is also conceivable that influenza-associated exacerbations of cardiac or pulmonary conditions are underappreciated in patients with complex presentations, which is a potential target for physician education and should be considered in guidelines for testing and treatment of influenza in this population. Patients who reported having received the influenza vaccine were less likely to be tested as well, though this was not a significant association in our model. In the United States, vaccination of adults for influenza tends to increase with increasing age, with adults over 65 years of age having the highest vaccination rates [16]. It is uncertain if providers consistently assess for and use vaccination information to guide clinical decisions, but this might contribute to lower rates of provider-ordered testing in more highly vaccinated populations. Additionally, studies have demonstrated an attenuation of influenza symptoms in adults who have been vaccinated, which may explain some differences in clinical presentation and lead to less provider-ordered testing in patients who were vaccinated [17, 18]

The proportion of patients tested at the academic center in our study was more than double that tested in the community hospitals, suggesting a difference in practices across inpatient settings that should be further examined. Another recent study of patients at an academic medical center observed high rates of testing in adults over 75 years of age and increased testing in those with high-risk conditions compared those without comorbidities [19]. The conflicting results of these two studies may reflect differences in testing practices in academic vs. community settings and between academic centers, which could be due to clinician factors, institutional practices, or test availability. These findings suggest the need to examine strategies that result in increased recognition of the need for testing.

A major concern regarding lower rates of influenza testing in older adults is that clinicians are underdiagnosing influenza in a population with substantial morbidity and mortality that could be mitigated by early antiviral treatment [1, 2, 20–22]. A better understanding of the factors involved in provider-ordered testing is needed to determine the barriers to early identification and treatment of infection. Early antiviral treatment improves outcomes and reduces rates of bacterial infection and other complications of respiratory viral illness, and positive tests can furthermore minimize overuse of antibiotics and unnecessary diagnostic workup [20–24].

Despite the current recommendation to use influenza antivirals within 48 hours of symptom onset, our study indicated that <3% of older patients presenting with an acute respiratory illness and only 11% of those with study-confirmed influenza received antivirals [13, 23]. Older adults may present later in illness with complications associated with influenza, leading clinicians to forego testing and treatment. This delay could also have implications for infection control. Activation of infection control measures that accompany provider-ordered influenza testing reduces nosocomial spread of infection, a benefit which is lost if clinicians do not identify those at risk in the elderly population.

An important consideration after decision to test for influenza is the choice of influenza diagnostic test employed. Rapid antigen tests have been shown to have poor sensitivity in hospitalized older adults, and previous high rates of false negatives may have led physicians to order fewer tests [24, 25]. Despite this, the majority of influenza tests ordered in our study were antigen detection, which may lead to missed cases and underdiagnosis of influenza in this population. The challenge of influenza diagnosis in hospitalized older adults is to not only identify cases clinically, but select an appropriately sensitive diagnostic test such as RT-PCR. This test is more sensitive than rapid diagnostic tests employed in the routine diagnostic laboratory, though also typically more costly which may limit its use [24, 25].

There are limitations to this study. The enrolled subjects were slightly younger than the unenrolled subjects, and thus the data may actually underrepresent cases of influenza in older adults. Subjects were enrolled at hospitals in Davidson County, TN and the conclusions may not be generalizable to other care settings including outpatient practices. Self-report of vaccination may not reflect actual immunization, although self-report has been demonstrated by others to be both reliable and readily obtainable [26]. Finally, increased availability of new more sensitive and rapid molecular diagnostics may impact testing practices in ways that were not examined in this manuscript.

Conclusions

Despite being at high risk for morbidity and mortality from influenza virus infection and sequelae, hospitalized older adults were tested for influenza less often than their younger counterparts, with testing performed in a minority of patients. No single factor accounts for decreased provider-ordered testing in this population, though differences in presentation including less influenza-like illness, attenuation of symptoms by vaccination, and higher burden of underlying cardiac and pulmonary disease may impact the decision of the provider to perform influenza testing. Further strategies are needed to increase clinician understanding of the challenges in clinically identifying influenza in older adults, as well as the limitations of diagnostic tests, to better diagnose and treat cases of influenza in this vulnerable population.

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Impact statement

We certify that this work is novel. While many have recognized the challenge of prompt recognition, diagnosis, and treatment of influenza virus infection in older adults, an examination of the demographic and clinical characteristics that influence influenza testing is lacking in the literature. Our study confirms that older adults are being undertested and underdiagnosed with influenza and identifies the clinical features complicating diagnosis for providers, thus highlighting areas of educational need and improvement.

Table 1

Characteristics of adults hospitalized with symptoms of respiratory illness or non-localizing fever by consent status.

Characteristic	**All patients (N = 2556) N (%)**	**No Consent (N=1134) N (%)**	**Consent (N=1422) N (%)**	**P-value (consented vs. not)**
Age, years (mean ± SD)	65 ± 17	67 ± 17	63 ± 17	< 0.001
Age group, years				
18–64	1204 (47)	464 (41)	740 (52)	<0.001
65+	1352 (53)	670 (59)	682 (48)	
Gender *				
Female	1502 (59)	647 (57)	855 (60)	0.003
Male	1046 (41)	479 (42)	567 (40)	
Race				
White	1009 (39)	448 (40)	561 (39)	0.96
Black	272 (11)	125 (11)	147 (10)	
Other	1275 (50)	561 (49)	714 (50)	
Insurance **				
No	87 (4)	25 (4)	62 (4)	0.057
Yes	1886 (94)	554 (95)	1332 (94)	
Unknown	31 (2)	3 (1)	28 (2)	
Fever				
No	1141 (45)	470 (41)	671 (47)	<0.001
Yes	992 (39)	248 (22)	744 (52)	
Unknown	423 (17)	416 (37)	7 (1)	

* N = 2548;

** N = 2004

Table 2

Characteristics of adults hospitalized with symptoms of respiratory illness or non-localizing fever and those with study-confirmed influenza by influenza testing status.

	All patients				Research laboratory confirmed influenza by RT-PCR			
Characteristic	All patients N = 1422 N (%)	Not tested N = 1023 N (%)	Tested N = 399 N (%)	P-value (tested vs. not tested)	All patients N = 136 N (%)	Not tested N = 59 N (%)	Tested N = 77 N (%)	P-value (tested vs. not tested)
Age, years (mean ± SD)	63 ± 17	66 ± 15	58 ± 18	<0.001	59 ± 19	56 ± 19	62 ± 18	0.028
Age group, years								
18–64	740 (52)	480 (47)	260 (65)	< 0.001	89 (65)	32 (54)	57 (74)	0.016
65+	682 (48)	543 (53)	139 (35)		47 (35)	27 (46)	20 (26)	
Sex								
Female	855 (60)	624 (61)	231 (58)	0.280	84 (62)	36 (61)	48 (62)	0.880
Male	567 (40)	399 (39)	168 (42)		52 (38)	23 (39)	29 (38)	
Race								
White	1000 (70)	730 (71)	270 (68)	0.220	83 (61)	41 (69)	42 (55)	0.160
Black	376 (26)	258 (25)	118 (30)		44 (32)	14 (24)	30 (39)	
Other	46 (3)	35 (3)	11 (3)		9 (7)	4 (7)	5 (6)	
Fever								
No	671 (47)	564 (55)	107 (27)	< 0.001	45 (33)	28 (47)	17 (22)	0.002
Yes	744 (52)	453 (44)	291 (73)		91 (67)	31 (53)	60 (78)	
Unknown	7 (0)	6 (1)	1 (0)		0 (0)	0 (0)	0 (0)	
ILI								
No	641 (45)	525 (51)	116 (29)	<0.001	28 (21)	19 (32)	9 (12)	0.003
Yes	781 (55)	498 (49)	283 (71)		108 (79)	40 (68)	68 (88)	
High-risk								
Cardiac	280 (20)	209 (20)	71 (18)	<0.001	19 (14)	9 (15)	10 (13)	0.360
Pulmonary	769 (54)	588 (57)	181 (45)		76 (56)	36 (61)	40 (52)	
Other	373 (26)	226 (22)	147 (37)		41 (30)	14 (24)	27 (35)	
Self-reported influenza vaccination status								

	All patients				Research laboratory confirmed influenza by RT-PCR			
Characteristic	**All patients N = 1422 N (%)**	**Not tested N = 1023 N (%)**	**Tested N = 399 N (%)**	**P-value (tested vs. not tested)**	**All patients N = 136 N (%)**	**Not tested N = 59 N (%)**	**Tested N = 77 N (%)**	**P-value (tested vs. not tested)**
Vaccinated	946 (67)	704 (69)	242 (61)	0.005	66 (49)	32 (54)	34 (44)	0.310
Not vaccinated	430 (30)	284 (28)	146 (37)		65 (48)	24 (41)	41 (53)	
Unknown	46 (3)	35 (3)	11 (3)		5 (4)	3 (5)	2 (3)	
Physician ordered test								
Negative	367 (26)	0 (0)	367 (92)	< 0.001	51 (38)	0 (0)	51 (66)	< 0.001
Positive	32 (2)	0 (0)	32 (8)		26 (19)	0 (0)	26 (34)	
Not performed	1023 (72)	1023 (100)	0 (0)		59 (43)	59 (100)	0 (0)	
Research lab flu status								
Negative	1280 (90)	961 (94)	319 (80)	< 0.001	0 (0)	0 (0)	0 (0)	
Positive	136 (10)	59 (6)	77 (19)		136 (100)	59 (100)	77 (100)	
Indeterminate	6 (0)	3 (0)	3 (1)		0 (0)	0 (0)	0 (0)	

Table 3

Independent factors associated with provider-ordered influenza testing among all adults hospitalized with symptoms of acute respiratory illness or non-localizing fever and among only those adults with research laboratory-confirmed influenza.

	All patients (N = 1422) AOR (95% CI)	Research flu test + patients (N = 1422) AOR (95% CI)
Age	2.02 (1.55–2.63)	1.47 (0.65–3.37)
No lung disease	1.68 (1.26–2.24)	1.65 (0.68–4.00)
ILI	2.22 (1.71–2.89)	3.43 (1.22–9.70)

Variables included in the multivariable model were age (as a continuous variable), race, insurance, underlying medical comorbidities (cardiac disease, COPD/asthma, and other high-risk conditions), ILI, self-reported vaccination status, and study year.